ISSN 2618-1584 Vol. 6, Issue 8: 43-46, DOI: 10.25236/FMSR.2024.060806

Research Progress of Remnant Cholesterol in Atherosclerotic Occlusive Disease

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Abstract: *Atherosclerotic occlusive disease (ASO) of the lower extremities is primarily caused by atherosclerosis of the lower extremities and is characterized by a state of reduced limb perfusion and metabolic disorders. Despite hemodialysis and medical care for the disease, many patients with ASO are at risk for recurrence, progression to severe limb ischemia, and increased rates of amputation in the patients. Remnant cholesterol (RC) is a strong predictor of ASO development and has been classified as a new atherosclerosis risk factor by the American Heart Association. RC induces endothelial dysfunction, stimulates inflammation and prothrombosis, and accelerates atherosclerosis formation, thereby promoting ASO development. This review summarizes the relevant definitions and detection methods of RC, the relationship between RC and ASO, and treatment methods. However, the definition and detection standard are still controversial. Further clarification of the correlation between RC levels and the occurrence and severity of ASO will provide some guidance for clinical diagnosis and treatment.*

Keywords: *Atherosclerotic occlusive disease; Atherosclerosis; Triglyceride; Remnant cholesterol*

1. Introduction

Atherosclerosis obliterans (ASO) of the lower limbs is a common peripheral vascular disease, affecting approximately 5.56% of the global population [1]. ASO of the lower limbs is a common peripheral vascular disease, affecting approximately 5.56% of the global population. ASO is caused by the narrowing or occlusion of arteries in the lower limbs, leading to reduced blood supply. This condition is a localized manifestation of systemic atherosclerosis. In severe cases, it may require amputation, resulting in significant economic burdens for patients and society, and is now a major public health issue. Early identification of residual cholesterol (RC) levels in ASO patients is crucial for early diagnosis and guiding treatment, which is essential for preventing lower limb vascular diseases.

The ankle-brachial index (ABI) is recommended as the primary screening tool for ASO in patients with multiple risk factors [2]. Although ABI has limited sensitivity in detecting early-stage ASO, it is particularly less sensitive in patients with severe atherosclerosis, such as those with diabetes or end-stage chronic kidney disease. When the ABI value is between 0.9 and 1.0, further examinations are necessary to confirm the diagnosis of ASO. Therefore, introducing a reliable, inexpensive, accurate, and easily accessible biomarker could overcome the limitations of ABI screening, thus improving the diagnosis and prognosis of ASO patients.

2. Definition and metabolism of remnant cholesterol

RC refers to the cholesterol content in triglyceride (TG)-rich lipoproteins[3]. These lipoproteins differ in density, volume, protein content, and core lipid composition. RC is categorized by fasting status: in the non-fasting state, it includes chylomicrons (CM), very low-density lipoproteins (VLDL), and intermediate-density lipoproteins (IDL); in the fasting state, it includes VLDL and IDL. In most individuals, CM is absent in plasma because lipoprotein lipase (LPL) rapidly hydrolyzes TGs, breaking down CM into chylomicron remnants. Therefore, RC levels are closely correlated with TG levels[4]. In plasma, TGs and total cholesterol (TC) are exchanged between high-density lipoproteins (HDL) and RC, leading to a negative correlation between HDL and RC levels. This exchange promotes the formation of macrophages and foam cells [5], accelerating the development of atherosclerosis.

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Lipoprotein lipase (LPL) is an enzyme anchored to endothelial cells in blood vessels. It acts independently of the physical state of apoB and serves as a bridge between LDL and proteoglycans. LPL is produced by adipocytes and muscle cells and expressed on the cell surface through heparan sulfate proteoglycans. It is then transported to capillary endothelium via glycosylphosphatidylinositol-anchored HDL-binding protein 1, influencing RC circulation. LPL is activated by apoC-II and apoA-V and inhibited by apoC-III. Mutations in LPL can lead to hypertriglyceridemia and accelerate atherosclerosis progression[6].

3. Epidemiology of RC and ASO

RC has a high correlation with atherosclerosis. In a prospective study, Duran[7] examined the relationship between RC, small dense LDL cholesterol (sdLDL-C) concentrations, and coronary heart disease outcomes, including myocardial infarction, ischemic stroke, and ASO. The study confirmed a close association between RC and ASO events. Song [8] conducted a retrospective analysis and found that diabetic patients with RC levels >0.64 mmol/L had an increased risk of ASO (sensitivity 71.9%, specificity 64.6%). Guan demonstrated a causal relationship between elevated RC levels and ASO using Mendelian randomization [9]。 Wadstrom and colleagues [10] conducted a prospective study showing that the incidence of ASO varies with RC concentration. For patients with RC <0.5 mmol/L, the incidence of ASO was only 2.9%, while in those with RC >1.5 mmol/L, the incidence was as high as 9.1%. After adjusting for multiple ASO-related risk factors, including LDL, the incidence of ASO in the latter group was five times higher than in the former. This indicates that RC has a stronger association with ASO occurrence compared to other manifestations of atherosclerotic cardiovascular disease.

4. Mechanism of RC causing atherosclerosis

Studies have shown that RC is a more accurate predictor of atherosclerosis risk compared to LDL, establishing it as a novel predictive marker [11]. Breslow's laboratory confirmed the potential atherogenic effects of RC using a gene-modified mouse model for advanced atherosclerotic lesions, the APOE-deficient mouse model [12], Genetic studies further validated RC's role in atherosclerosis and its complications [13]. RC may contribute to the progression of atherosclerosis through various pathways.

4.1 Lipid Metabolism Disorders

Research indicates that the progression of atherosclerosis is primarily driven by the TC content in RC, rather than the TG itself. Elevated RC levels are one of the markers of atherogenic dyslipidemia[14].RC is a critical indicator of lipid metabolism. Elshazly[15] analyzed data from 5,754 patients and found that even after adjusting for C-reactive protein (CRP) levels, RC remained an independent risk factor for the progression of atherosclerosis. Each RC particle contains about 40 times more cholesterol than LDL. Lipoproteins entering the arterial intima bind to proteoglycans in the extracellular matrix under the action of lipoprotein lipase, becoming trapped in the arterial wall. They can be directly absorbed by macrophages, and RC does not need oxidative modification to induce atherosclerosis[16].Therefore, the cholesterol content in RC may have a stronger atherogenic potential than that in LDL.

4.2 Endothelial Cell Injury

In ASO, ischemia-reperfusion injury triggers inflammation, promotes an increase in reactive oxygen species (ROS), thereby leading to endothelial dysfunction [17]. The vascular endothelium acts as a highly selective barrier to control vascular permeability and regulate vascular tone.RC promotes endothelial dysfunction by increasing the production of ROS, leading to homeostatic changes in the characteristics and functions of endothelial cells[18]. RC can enter endothelial cells through endocytosis, and when endothelial cells are injured, it accelerates the development of atherosclerosis.

4.3 Chronic Inflammation

Researchers, including Anette[19]examined the link between RC and inflammation by analyzing clinical data from 60,608 participants in Copenhagen. Their Mendelian trial revealed that a 1 mmol/L increase in RC levels corresponded to a 37% rise in C-reactive protein (CRP) levels, whereas low-density lipoprotein (LDL) levels increased by only 7%. This finding suggests that elevated RC levels are more closely associated with low-grade inflammation compared to LDL. The pro-inflammatory impact of RC

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particles is significantly greater than that of LDL ($P<0.05$), and RC particles are not regulated or absorbed by macrophage scavenger receptors [20]. Furthermore, low-grade inflammation contributes significantly to the formation, progression, and rupture of arterial plaques, thereby exacerbating atherosclerosis.

4.4 Prothrombotic and Thrombotic Effects

In dysfunctional endothelial cells, RC stimulates the secretion of tissue factor from both endothelial cells and monocytes. Tissue factor is a critical initiator of the coagulation cascade, activating it and platelets through the assembly of the prothrombin complex[21]. This process increases the expression of plasminogen activator inhibitor-1, which reduces fibrinolysis, enhances platelet activation and aggregation, and contributes to a pro-thrombotic state[22].Overall, these mechanisms lead to increased platelet aggregation and clot formation, playing a significant role in the progression of atherosclerotic lesions.

5. Treatment of RC

The EAS/EFLM guidelines [23] recommend incorporating laboratory parameters for RC as part of routine lipid analysis. Currently, in many patients undergoing treatment for atherosclerotic vascular disease, the primary criterion for lipid abnormalities is no longer elevated LDL, but rather elevated RC and HDL.

There are currently no specific guidelines or expert recommendations for drug treatments targeting RC.While medications such as statins, fibrates, niacin, omega-3 fatty acids, and high-purity fish oil preparations are used to lower total TC or TG, there are no drugs specifically aimed at reducing RC levels.

Statins lower RC levels by inhibiting TC synthesis, which leads to an increase in LDL receptors in liver cells and VLDL receptors in muscle and adipose tissue [23], Additionally, statins have anti-inflammatory effects, as they reduce CRP, stabilize atherosclerotic plaques, and prevent plaque rupture.

Pemafibrate, a novel selective peroxisome proliferator-activated receptor (PPAR-α) agonist, is used in fibrate medications. PPAR-α is a nuclear receptor that increases the expression of LPL, apo-AI, and other lipid-related genes. Studies have shown that pemafibrate is more effective in lowering TG, possibly due to its more effective inhibition of apoC-III on LPL [24]. The PROMINENT trial, which involved 10,497 participants, found that pemafibrate treatment reduced TG levels by 26% and RC levels by 26%, but LDL levels increased by 12.3% and apo-B levels increased by 4.8% [25]. These results indicate that pemafibrate significantly lowers TG and RC levels, suggesting that RC conversion to LDL is relatively high and not directly cleared from the circulation[4].

6. Conclusions

RC can accumulate in the arterial intima and is an important predictor in atherosclerosis. Prolonged high levels of RC increase the incidence of vascular diseases [26].RC is a major pathogenic factor accelerating the progression of atherosclerosis. Although pharmacological therapies can significantly reduce the risk of atherosclerosis, there remains a risk of recurrence. Early identification of RC levels in ASO is crucial for early diagnosis and treatment guidance, which is essential for preventing lower limb vascular diseases. Therefore, a deeper understanding of the relationship between ASO and RC can help discover new treatment approaches for ASO and provide a theoretical basis for exploring novel drugs and therapeutic targets.

Acknowledgements

Project name: College Level Project of the First Affiliated Hospital of Xi'an Medical University: Analysis of the efficacy of balloon dilatation for non-thrombotic iliac vein compression syndrome; project number :(XYYFY-2023-04)

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